PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference VT/91-22814	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/50992	International filing date *(day/month/year)* 12.12.2003	Priority date *(day/month/year)* 20.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D209/00		
Applicant CIBA SPECIALTY CHEMICALS HOLDING INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.06.2004	27.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Gavriliu, D Telephone No. +49 89 2399-8274

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50992

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-65	as originally filed

Claims, Numbers

1-15, 17-24, 32, 36	as originally filed
16, 25-31, 33-35	received on 13.07.2004 with letter of 12.07.2004
37-40	received on 06.09.2004 with letter of 02.09.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-17, 25, 26-30(part.),36-40(part.) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17, 25, 26-30(part.),36-40(part.)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17, 25, 26-30(part.), 36-40(part.)
Industrial applicability (IA)	Yes:	Claims	1-17, 25, 26-30(part.), 36-40(part.)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV

Lack of unity of invention

The separate inventions of the present application are:

1. Further 3-hydroxyindol derivatives of formula (I) or (II), their manufacture, intermediates, derivatives and pharmaceutical uses (Claims 1-17, 25, 26-30(part), 36-40(part)).

2. Further indole derivative of formula (XII), their manufacture, intermediates, derivatives and pharmaceutical uses (Claims: 18(part), 19-20, 24(part.), 26-30(part), 33-34, 36-40(part.)).

3. Further indole derivative of formula (XIV), their manufacture, intermediates, derivatives and pharmaceutical uses (Claims: 18(part.), 21, 22-23, 24(part), 26-30(part), 31, 32, 35, 36-40(part.)).

The subject-matter of the present application relates to compounds of formulae (I), (II), ((III*), (VII), (VIII), (Xa), (Xb), (XI), (XII), (XIV)(XIV), (XIIIa), (XVI), (II^1), XII^1, XIV^1, II^2, XII^2, XIV^2, II^3, XII^3, XIV^3, II^4, XII^4, II^5, XII^5, XX^7, XXI*, XXI** (Claims 5, 6, 9, 17, 20, 23, 32, 36) and to different processes to prepare these compounds or to processes in which the above-mentioned compounds are involved. The structural element shared by all the alternatives falling within the scope of Claims 5, 6, 9, 17, 20, 23, 32 and 36 is the indole ring substituted in position 3. A further unifying feature is the use of these compounds as pharmaceutical agents (e.g. for treating migraine). However, according to Rule 13.2 PCT the special technical features providing a link between inventions (Rule 13.1 PCT) must make contribution over the prior art (Rule 13.2 PCT). This requirement is not fulfilled in the present case since the documents US 5037845(see column 2-lines 9-27), WO 9118897 (see Claims 1 and 10) and Tetrahedron 58 (2002) 8399-8412 (see page 8399 and table 1)(documents cited by the Applicant in the present description) disclose indole derivatives substituted in position 3 useful as pharmaceuticals (e.g. the compounds disclosed by US 5037845 are useful to treat migraine conditions as in the present Claims 37-40). Consequently, both common features of the inventions 1-3 are not new over the prior art.

The present intenational application contents 3 inventions, but since the Applicant

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

It should be understood 5that the following comments refer only to invention 1(see pint IV).

1. **Reference is made to the following documents:**

D1: US-A-6 114 536 (TORU ESAKI ET AL.) 5 September 2000 (2000-09-05)
D2: US-A-5 037 845 (Glaxo Group Limited England) 6 August 1991 (1991-08-06)
D3: Tetrahedron, 58 (2002), 8399-8412-"A versatile synthetic methodology for the synthesis of tryptophols

2. **Amendments** (Article 19.2 PCT)

The amendments of the Claims 16, 25-31, 33-35 filed with the letter of 12.07.2004, relate to "a method for the synthesis of a tryptamine derivative having pharmacologically useful properties" claimed additionally to the originally claimed methods. The above-mentioned amendments seem to fulfill the requirements of Article 19(2) PCT. The amendments filed with the letter of 02.09.2004 relate to extra new 4 claims directed to the use of the claimed compounds (Claims 5, 6, 9, 17, 20, 23, 32, 36) for the manufacture of pharmaceuticals for the treatment of migraine. These objections seem not to fulfill the requirements of Article 19(2) PCT, because were not originally disclosed.

3. **Novelty** (Article 33(1) and (2)PCT)

The present subject-matter seems to be novel over the cited prior art on the account of the provisio for the claimed compounds and on the account of the intermediate (III) for the Claim 1.

4. **Inventive step** (Article 33(1) and (3)PCT

The present subject-matter relates to indole derivative or 2-oxo-indole derivative and to processes in which those compounds are involved.

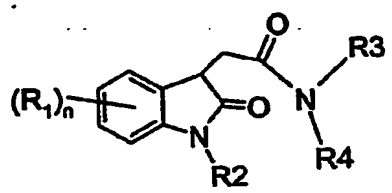
D3 disclosed the synthesis of 3-hydroxy-2-oxiindole-3-yl acetate through the reaction of an isatine derivative and malonic acid in pyridine (see D3 page 8403

and table 1). The above-mentioned compound is further reduced or is further used as starting material for different reactions. D1 discloses the synthesis of the 3-hydroxy-2-oxiindole-3-yl acetamide from the corresponding acetate(see Do-column 8). In view of the reaction disclosed by D1 and D3 the present claimed subject-matter seems not to involve an inventive step.

Re Item VIII

Certain observations on the international application

The Claims 16, 25-31, 33-35 claimed a method for this synthesis of a tryptamine derivative having pharmaceutical useful properties. The above-mentioned claims do not meet the requirements of Article 6 PCT in that the matter for which the protection is sought is not clearly defined. This functional definition does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific methods fall within the scope of the said claims. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful examination impossible.

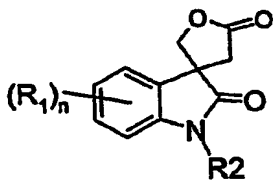


(Xb)

wherein n, R_1, R2, R3 and R4 are as defined for a compound of the formula Xa in claim 13.

15. A method according to any one of claims 1 to 4, where a compound of the formula Xb as defined in claim 14 is obtained by hydrogenation of the benzylic 3-hydroxy group in a compound of the formula II.

16. A method for the synthesis of a tryptamine derivative having pharmacologically useful properties, or a method for preparing a spiro indole of the formula XI,



(XI)

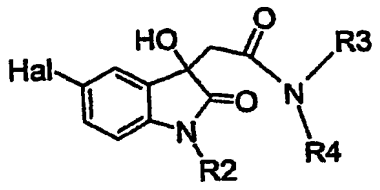
comprising converting a compound of the formula Xb as defined in claim 14 to a spiro indole of the formula XI by reaction with formaldehyde or a precursor thereof,
wherein n, R1 and R 2 are as defined in claim 14.

17. A compound of the formulae VII or VIII as defined in claim 11 or of the formula IX as defined in claim 12 or of the formula Xa as defined in claim 13 or of the formula Xb as defined in claim 14 or of the formula XI as defined in claim 16. .

18. A method according to any one of claims 1 to 3, further comprising reducing a compound of the formula II wherein n, R2, R3 and R4 are, independently of each other, as defined in claim 1, and R_1 is unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, alkylsulfonyl, sulfonyl alkyl, N-mono- or N,N-disubstituted or unsubstituted aminosulfonyl alkyl, hydroxy, mercapto, nitro, halogen, cyano, carboxamido, N-mono- or N,N-disubstituted carboxamido, unsubstituted or substituted alkoxycarbonyl, unsubstituted or subsituted alkoxy, formyl or other alkanoyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted

of the corresponding acyl moieties; or the silyl derivatives are introduced using the corresponding silylhalogenides, respectively; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said conversion.

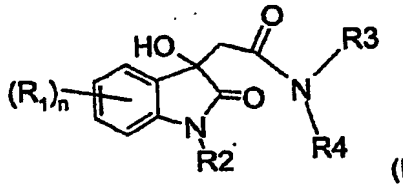
25. A process for the introduction into a compound of the formula II as defined in claim 18 where n is zero and the other substituents are as defined in claim 1 or 3, of a moiety R_1 resulting from electrophilic substitution reaction with a halogen R_1 by reaction with a halo-succinimide, or nitro by reaction with nitric acid, leading to a compound of the formula XVI,



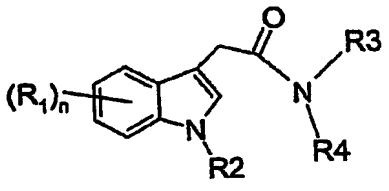
(XVI)

wherein Hal is nitro or halogen, and R2, R3 and R4 have the meanings given for a compound of the formula II; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

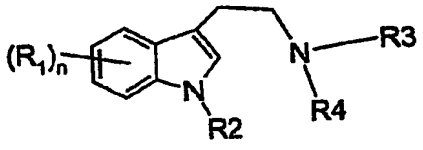
26. A process for the manufacture of a compound of the formula II^1, XII^1 or XIV^1, respectively,



(II^1)



(XII^1) or



(XIV^1),

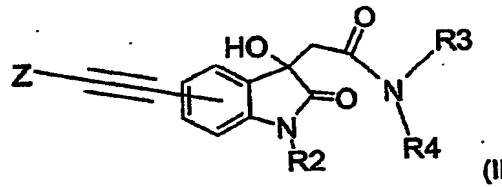
wherein n is 1 or 2, R_1 is unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl and R2, R3 and R4 have the meanings given under formula II in claim 1 or 3, comprising reacting a compound of the formula II as defined in claim 18 for the synthesis of compound II^1, or of the formula XII as defined in any one of claims 19, 20 or 24 for the synthesis of compound XII^1, or of the formula XIV as defined in any one of claims 22, 23 or

24 for the synthesis of compound XIV^1, wherein in each case n is 1 or 2 and R1 is halogen, under the conditions of the Suzuki coupling or analogous conditions with a compound of the formula (A),

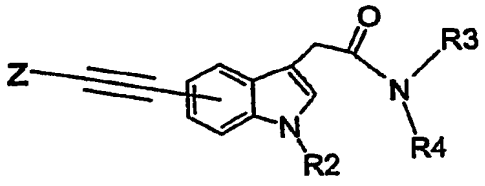
$$Ar\text{-}BY_2 \qquad (A)$$

wherein Ar is unsubstituted or substituted aryl or heterocyclyl and Y is OH, into the corresponding compounds of the formulae II^1, XII^1 or XIV^1, respectively; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

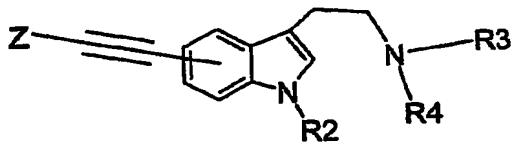
27. A process for the reaction of a compound of the formula II as defined in claim 18, of the formula XII as defined in any one of claims 19, 20 or 24, or of a compound of the formula XIV as defined in any one of claims 22, 23 or 24, with the proviso that in each of the compounds of the formulae II, XII and XIV, n is 1 and R1 is halogen, to a compound of the formulae II^2 from compound II, to a compound of the formula XII^2 from compound XII or to a compound of the formula XIV^2 from compound XIV, respectively,



(II^2),



(XII^2) or



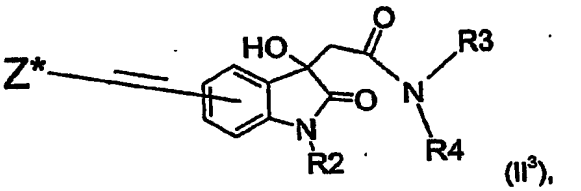
(XIV^2),

wherein Z is unsubstituted or substituted alkyl, and R2, R3 and R4 are as defined under formula II, respectively, by coupling under the conditions of or analogous to a Sonogashira coupling with a compound of the formula (B),

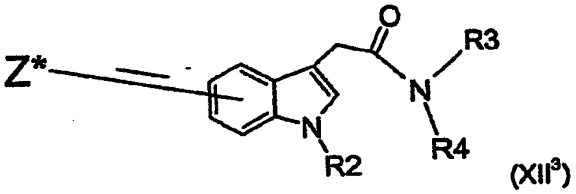
(B)

wherein Z is unsubstituted or substituted alkyl, to yield the corresponding compounds of the formulae II^2, XII^2 or XIV^2, respectively; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

28. A process for the reaction of compounds of the formula II as defined in claim 22, of the formula XII as defined in any one of claims 19, 20 or 24, or of compounds of the formula XIV as defined in any one of claims 22, 23 or 24, with the proviso that in each of the compounds of the formulae II, XII and XIV n is 1 and R1 is halogen, to compounds of the formulae II^3 (from compound II), XII^3 (from compound XII) or XIV^3 (from compound XIV) respectively,

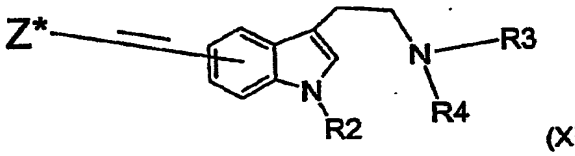


(II^3),



(XII^3)

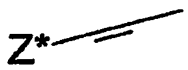
or



(XIV^3),

wherein Z* is unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted arylsulfonyl, unsubstituted or substituted alkylsulfonyl, $(Y)_2N$-sulfonyl wherein each Y, independently of the other, is hydrogen or unsubstituted or substituted alkyl; or Z* is alkoxycarbonyl, cyano or unsubstituted or substituted heterocyclyl, and R2, R3 and R4 are as defined for compounds of the formula II,

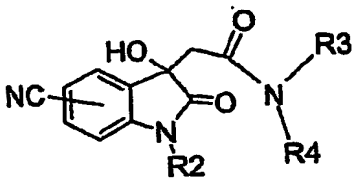
by coupling with a compound of the formula (C),



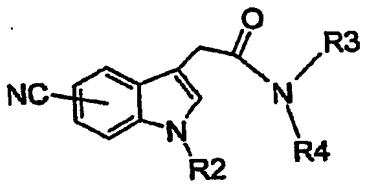
(C)

wherein Z* is as just defined under conditions of or analogous to the Heck reaction to yield the corresponding compounds of the formulae II^3, XII^3 or XIV^3, respectively; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

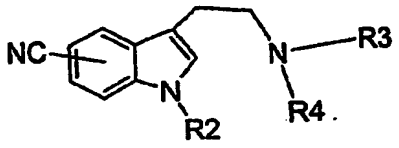
29. A process for the reaction of compounds of the formula II as defined in claim 22, of the formula XII as defined in any one of claims 19, 20 or 24, or of compounds of the formula XIV as defined in any one of claims 22, 23 or 24, with the proviso that in each of the compounds of the formulae II, XII and XIV n is 1 and R1 is halogen, to compounds of the formulae II^4 (from compound II), XII^4 (from compound XII) or XIV^4 (from compound XIV) respectively,



(II^4),



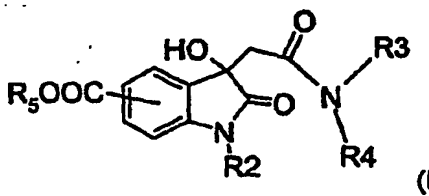
(XII^4) or



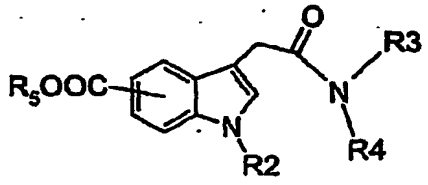
(XIV^4),

wherein R2, R3 and R4 are as defined above for a compound of the formula II, by reaction with a cyanide salt in the presence of a palladium catalyst; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process..

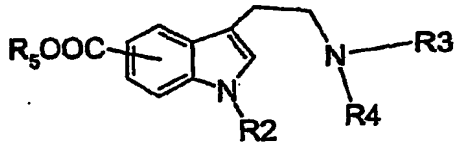
30. A process for the reaction of compounds of the formula II as defined in claim 22, of the formula XII as defined in any one of claims 19, 20 or 24, or of compounds of the formula XIV as defined in any one of claims 22, 23 or 24, with the proviso that in each of the compounds of the formulae II, XII and XIV n is 1 and R1 is halogen to compounds of the formulae II^5 (from compound II), XII^5 (from compound XII) or XIV^5 (from compound XIV) respectively,



(II^5),



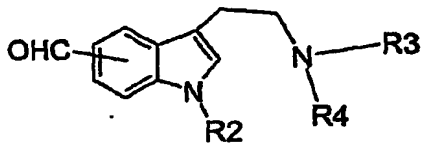
(XII^5) or



(XIV^5),

wherein R_5 is unsubstituted or substituted alkyl, or unsubstituted or substituted aryl, and R2, R3 and R4 are as defined for the compounds of the formula II, by reaction with CO in the presence of the corresponding alcohol R_5-OH; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

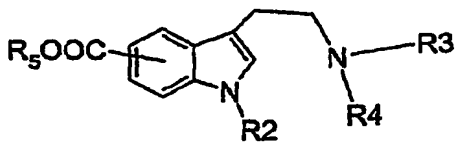
31. A process for the reaction of a compound of the formula XIV as defined in any one of claims 22, 23 or 24 where n is 1 and R1 is halogen, comprising converting it into the corresponding compound of the formula XX^6,



(XX^6),

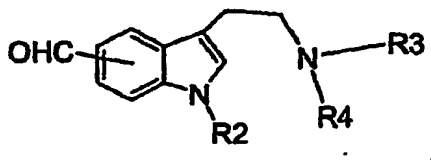
wherein R2, R3 and R4 are as defined for the compound of the formula XIV, by reaction with first a lithium alkyl compound to form the lithio derivative and then with DMF or triethyl formate, to obtain the compound of the formula XX^6 after hydrolysis; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

32. A compound of the formula XIV^5



(XIV^5),

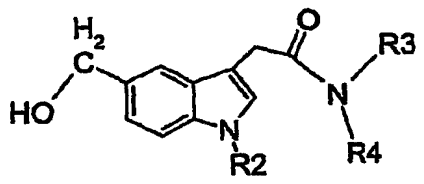
or of the formula XX^6



(XX^6),

wherein R2, R3, R4 and R_5 are as defined in claim 1 for formula II, provided that one of R3 or R4 is not methyl and R3 and R4 together are not phthalyl, or a salt thereof.

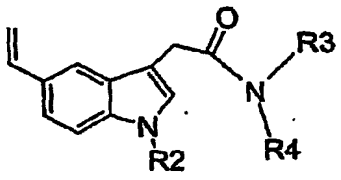
33. A process for the manufacture of a compound of the formula XXI**



(XXI**)

wherein R2, R3 and R4 have the meanings indicated for compounds of the formula XX^6 in claim 31, by reduction of the compound of the formula XX^6 in the presence of a selective transition metal catalyst; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

34. A process for the manufacture of a compound of the formula XXI*,



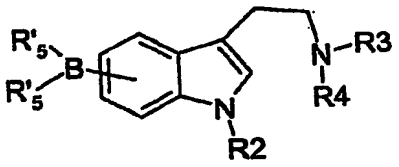
(XXI*)

wherein R2, R3 and R4 have the meanings indicated for compounds of the formula XX^6 in claim 31,

by conversion of a compound of the formula XX^6 as defined in claim 31 into the corresponding compound of the formula XXI* by reaction with a Wittig or Wittig Horner

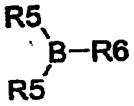
reagent in the presence of a suitable base; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

35. A process for the reaction of a compound of the formula XIV as defined in any one of claims 22, 23 or 24 where n is 1 and R_1 is halogen, comprising converting it into the corresponding compound of the formulae XX^7,



(XX^7)

wherein R2, R3 and R4 are as defined for the compound of the formula XIV, and each of R'_5 independently is hydroxy or an alkoxy residue of a lower alcohol, or the 2 residues R'_5 together are C_2-C_8alkylene-dioxy,
by reaction with first a lithium alkyl compound to form the lithio derivative, and then with an ester of boric acid B,



(B)

wherein each of R5 and R6 independently is an alkoxy residue of a lower alcohol, or the 2 residues R5 together are C_2-C_8alkylene-dioxy,
and subsequent hydrolysis, to obtain the compound of the formula XX^7; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

36. A compound of any of the formulae XIIIa, XVI, II^1, XII^1, XIV^1, II^2, XII^2, XIV^2, II^3, XII^3, XIV^3, II^4, XII^4, II^5, XII^5, XX^7, XXI* or XXI** as defined in claims 21, 25, 26, 27, 28, 29, 30, 33, 34, 35, or a salt thereof.

37. Use of a compound according to one of the claims 5, claim 6, claim 9, claim 17, claim 20, claim 23, claim 32 or claim 36 for the manufacture of a pharmaceutical.

38. Use of a compound according to one of the claims 5, claim 6, claim 9, claim 17, claim 20, claim 23, claim 32 or claim 36 for the manufacture of a pharmaceutical intended for the treatment and/or prevention of migraine conditions.

39. Use of a compound according to one of the claims 5, claim 6, claim 9, claim 17, claim 20, claim 23, claim 32 or claim 36 for the manufacture of a tryptamine derivative.

40. Use of a compound according to one of the claims 5, claim 6, claim 9, claim 17, claim 20, claim 23, claim 32 or claim 36 for the manufacture of a tryptamine derivative pharmaceutical intended for the treatment and/or prevention of migraine conditions.